REMARKS

Claim Amendments

Claims 1-8 were examined. Claims 2, 6 and 7 have been cancelled. Claim 1 has been amended. In particular, Claim 1 has been amended to recite that the sustained release composition is in an injectable form; that the polymer of the sustained release composition is a poly(lactide-co-glycolide); and that for the bisphosphonate of Formula I, X is-OR_1, R_2 is $(CH_2)_n$, branched alkylene, branched or straight alkenylene or alkynylene and Y is H, alkyl, aryl, heteroaryl, amino, cyano or amido. As such, the bisphosphonate of the sustained release composition are geminal bisphosphonates where one of the substituent X on the carbon atom common to the phosphonate groups, is either a hydroxy group or an ether group. Support for these amendments can be found in the originally filed claims. No new matter is added as a result of these amendments.

Rejection of Claim 8 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claim 8 under 35 U.S.C. § 112, First Paragraph. In particular, the Examiner stated that there is no original disclosure supporting the recitation in Claim 8 that the concentration of the bisphosphonate is from about 0.5% (w/w) to about 20% (w/w) of the total weight of the composition. Applicants respectfully disagree.

At page 17, lines 21-27, the specification teaches that the invention relates to a composition for the sustained release of bishphosphonates comprising a biocompatible polymer matrix having a therapeutically effective amount of bisphosphonate incorporated therein. At page 11, lines 18-20, the specification teaches that a therapeutically effective amount is that amount needed to elicit the desired biological response following administration. Further, at page 9, line 21-page 10, line 3, the specification teaches that the desired therapeutic effect depends on the planned release levels and time over which release occurs with a preferred range of microparticle loading between about 0.5% (w/w) to about 20% (w/w). Finally, microparticles containing a load of bisphosphonate within this range (e.g., 1% and 2.5% w/w) were prepared (see page 22, lines 25-27). As such, the specification clearly conveys to one of skill in the art that the concentration of bisphosphonate present in the sustained release compositions described

in the specification can range from 0.5% (w/w) to about 20% (w/w). Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 2 and 8 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 1, 2 and 8 under 35 U.S.C. § 112, second paragraph as being indefinite. In particular, the Examiner correctly noted that R_2 cannot be H or N. The definition of R_2 in Claim 1 has been amended to no longer include H or N. As such, the rejection is overcome.

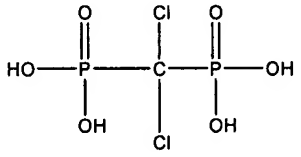
Rejection of Claims 1-8 for Obviousness-type Double Patenting

The Examiner has rejected Claims 1-8 for obviousness-type double patenting over Claims 1-58 of U.S. Patent No. 6,558,702. A Terminal Disclaimer in accordance with the requirements of 37 C.F.R. § 1.321(c) is being filed concurrently. As such, the rejection is obviated.

Rejection of Claim 1 Under 35 U.S.C. § 102(b)

The Examiner has rejected Claim 1 under 35 U.S.C. § 102(b) as being anticipated by D'Souoza *et al.* (Drug Devleopment and Industrial Pharmacy, Vol. 25, pages 591-596). In particular, the Examiner stated that D'Souza *et al.* teach a microsphere composition having clodronate encapsulated in crosslinked albumin.

As a preliminary matter, clodronate has the following chemical structure:



Claim 1 has been amended to recite that for Formula I, X is $-OR_1$, R_2 is $(CH_2)_n$, branched alkylene, branched or straight alkenylene or alkynylene and Y is H, alkyl, aryl, heteroaryl, amino, cyano or amido. As such, the carbon atom of Formula I, which is common to the geminal phosphonate groups, bears substituents (X and Y or R_2-Y) neither of which is chlorine and which are also different from each other. In contrast, D'Souza *et al.* teach the encapsulation of the bisphosphonate (clodronate), wherein the substituents on the carbon atom common to the

phosphonate groups are the same (chlorine). As such, D'Souza *et al.* do not teach or suggest the bisphosphonates embraced within Formula I of Claim 1, as amended. Hence, the teachings of D'Souza *et al.* do not anticipate Claim 1, as amended.

In addition, Claim 1 has been amended to recite that sustained release composition comprises a poly(lactide-co-glycolide) polymer. In contrast, the microspheres of D'Souza *et al.* have albumin as the polymer matrix. As such, the teaching of albumin microspheres by D'Souza *et al.*, do not anticipate the poly(lactide-co-glycolide) microparticles of amended Claim 1.

In view of the above, Claim 1 is not anticipated by the teachings of D'Souza *et al.* and meets the requirement of 35 U.S.C. 102(b). Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claim 8 Under 35 U.S.C. § 103(a)

The Examiner rejected Claim 8 under 35 U.S.C. § 103(a) as being obvious over the teachings of D'Souza *et al.* In particular the Examiner stated that although D'Souza *et al.* do not teach the bisphosphonate concentration recited in Claim 8, that determination of the concentration would have been obvious to one of ordinary skill in the art.

Claim 1, from which Claim 8 depends, has been amended to recite bisphosphonates which are distinct in structure from the clondronate taugth by D'Souza *et al.* Since D'Souza *et al.* neither teach nor suggest the bisphosphonates embraced within amended Claim 1, they cannot make obvious a range for the bisphosphonates embraced within Claim 1. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-4 and 8 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-4 and 8 under 35 U.S.C. § 103(a) as being obvious over European Patent Application 839,525 (hereinafter the '525 Application). In particular, the Examiner stated that the '525 Application describes, but does not exemplify, sustained release compositions comprising lactic acid and a bone resorption suppressor. Further, the Examiner stated that the mention of alendronate or residronate as bone resorption agents, which can be encapuslated, makes the invention of Claims 1-4 obvious. Finally, the Examiner stated that the

range recited in Claim 8, although not specifically taught in the '525 Application, would be obvious to one of ordinary skill in the art. Applicants respectfully disagree.

The '525 Application teaches sustained release compositions wherein the polymer is a homopolymer of lactic acid. In fact, the polylactic acid used in the invention is hydrolyzed polylactic acid. At page 4, lines 34-36, the '525 Applications teaches that use of hydrolyzed lactic acid provides a preparation with a small initial burst as compared to sustained release composition having polylactic acid produced by ring-opening polymerization (page 4, lines 34-36). Although the sustained release composition taught in the '525 Application can have a wide variety of active substances encapsulated, the polymer of the composition must be lactic acid (see page 9, lines 55-56), preferably hydrolyzed to provide a desirable composition (small initial burst). As such, the '525 Application does not teach or suggest the use of polymers other than lactic acid in the described sustained release compositions. In fact, based on the teaching of the '525 Application, one of skill in the art would have no reasonable expectation of achieving a sustained release composition, having a desired release profile (e.g., small initial burst), using anything but the hydrolyzed form of lactic acid.

In contrast, Applicants' sustained release composition, as presently claimed, comprises a poly(lactide-co-glycolide) as the polymer. The '525 Application does not teach or suggest the use of poly(lactide-co-glycolide). In fact, the '525 Application could be considered a teaching away of any polymer other than hydrolyzed lactic acid homopolymer, since the hydrolyzed lactic acid results in compositions with small initial bursts as compared to unhydrolyzed lactic acid (page 4, lines 34-36). In other words, the '525 Application teaches the use of the lactic acid homopolymer, and the advantages (small burst) of a hydrolyzed version of the lactic acid homopolymer. As such, one or ordinary skill in the art upon reading the '525 Application would be taught that the hydrolyzed form of the lactic acid provides a desired release profile, even as compared to unhyrolyzed lactic acid, and should be used to achieve a desired release profile (small initial burst). The motivation to employ polymers with a repeat unit other than lactic acid is absent.

In view of the above, Claims 1-4 and 8 meet the requirements of 35 U.S.C. 103(a) and are patentable over the teaching of the '525 Application. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 5-7 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 5-7 under 35 U.S.C. § 103(a) as being obvious over the '525 Application as applied to Claims 1-4 and 8 and further in view of Asgharnejad *et al.* (U.S. Patent No. 6,123,964) or Bechard (U.S. Patent No. 5,431,920). In particular, the Examiner stated that Asgharnejad *et al.* and Bechard teach that pamidronate, etidronate and tiludronate are know pharmaceutical agents used to inhibit bone resorption. The Examiner relies on these teachings in Asgharnejad *et al.* and Bechard to cure the deficiencies in the '525 Application of not mentioning these agents as examples of bone resorption agents. The deficiencies of the '525 Application, however, are far more extensive than the specific mention of pamidronate, etidronate and tiludronate as bone resorption agents and are not cured by Asgharnejad *et al.* and Bechard.

As a preliminary matter, Claims 6 and 7 have been cancelled. As such, the rejection will be addressed only with respect to remaining Claim 5.

As discussed in detail above, although the '525 Application teaches sustained release compositions with a wide variety of active agents, the polymer of the composition is limited to lactic acid, preferably hydrolyzed lactic acid in order to achieve a desired release (small initial burst) of agent (see page 9, lines 55-56 and page 4, lines 34-36). The use of polymers other than lactic acid homopolymer is neither taught nor suggested. In fact, one of ordinary skill in the art would not be motivated to use polymers other than hydrolyzed lactic acid, since even unhydrolyzed lactic acid is taught as resulting in a large initial burst (page 4, lines 34-36).

Asgharnejad *et al.* and Bechard are being relied upon for teaching the specific bisphosphonate, pamidronate, not found in the '525 application. However, neither Asgharnejad *et al.* nor Bechard teach sustained release compositions. Rather, Asgharnejad *et al.* and Bechard teach a wet granulation formulation and enteric coated oral formulations, respectively. As such, Asgharnejad *et al.* and Bechard cannot cure the lack of a teaching or suggestion in the '525 Appication to use a polymer other than a lactic acid homopolymer in a sustained release composition of a bisphosphonate. As such, Claim 5 meets the requirements of 35 U.S.C. 103(a) in view of the '525 Application either alone or in combination with Asgharnejad *et al.* and/or Bechard.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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